Remarks

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-36 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner objected to the term "administering" in claim 1 and requested clarification. In response, claim 1 has been amended to specify that the complex contacts the cell in vivo. Support for this amendment can be found in the specification at least at page 10, lines 14-15. Claim 1 has been further amended to replace the term "administering" with "contacting" to allow for the dependent claims to more clearly reference claim 1. Support for this amendment can be found in the specification at least at page 10, lines 14-16.

The Examiner objected to the term "composition" in claim 24. In response, claim 24 has been amended to correct this typographical error and refer to the "compound".

The Examiner objected to the phrase "contacting steps" in claim 28 and requested clarification. In response, Applicants respectfully point out that claim 28 is a dependent claim, which directly depends from claim 14 and indirectly depends from claim 1. Claim 1 specifies that the contacting step occurs between the complex and the cell *in vivo*. Claim 14 further specifies that the cell is in pulmonary tissue. As a dependent claim, claim 28 contains all of the limitations of claims 1 and 14. Thus, contrary to the Examiner's assertion, claim 28 is clear, in particular with respect to when, where and what is being contacted in the "contacting steps".

Therefore claims 1, 24 and 28 and the claims that depend there from are definite.

Rejection Under 35 U.S.C. § 102

Claims 1-6, 8-18, 20-24, 26, 28, and 33-36 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,071,497 to Steiner, *et al*. ("the '497 patent") and claims 1-2, 4-10, and 13-36 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,652,885 to Steiner, *et al*. ("the '885 patent"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

For a rejection of claims to be proper under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to make and use the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled". *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 U.S.P.Q.2d 1385, 1416 (Fed. Cir. 2003).

To establish inherency, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably

support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis added).

The claimed methods

Claim 1, the sole independent claim in the pending application, defines a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer. The method requires forming a complex comprising the compound and an effective amount of diketopiperazine (DKP) to enhance transport of the compound directly into the cell, wherein transport of the compound is increased in the presence of the DKP compared to in the absence of the DKP, and contacting the cell *in vivo* with the complex.

As discussed in more detail below, the references cited by the Examiner do not disclose or suggest enhancing transport across a cell membrane and delivering of a compound directly into a cell.

The '497 patent

The '497 patent describes a drug delivery system comprising a complex of diketopiperazine and drug to be delivered. The '497 patent discloses administration of the drug to the pulmonary system (*see e.g.* abstract). In Example 1, the '497 patent discloses a study of the administration of salmon calcitonin (sCT)-diketopiperazine microparticles to sheep. Following instillation of the microparticles in each lung of the sheep, the blood was sampled, collected, and analyzed to determine that blood plasma concentrations of sCT. These results

were compared to the blood plasma concentrations of sCT obtained following subcutaneous injection of sCT. The results showed rapid absorption of sCT into blood plasma following administration to the lung and via subcutaneous injection (col. 11, lines 62-64).

However, a discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. As discussed in, Patton, et al., "*The Lungs as a Portal of Entry for Systemic Drug Delivery*", Proc. Amer. Thorac. Soc., 1:338-344 (2004) ("Patton") (a copy of which is enclosed), the "precise mechanisms of macromolecule absorption in the lungs are not well known." (*Id.*, page 341, right col., first full para.) Patton indicates that generally "exogenous macromolecules are thought to be absorbed from the airspaces nonspecifically". (*Id.*) Thus, the mere disclosure in the '497 patent regarding the blood serum levels of calcitonin does not disclose or suggest administration into a cell, let alone that a complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer. Therefore, claims 1, 3-6, 8-18, 20-24, 26, 28, and 33-36, as amended, are not anticipated by the '497 patent.

The '885 patent

The '885 patent describes a method for purifying peptides and proteins by incorporating them into diketopiperazines to facilitate removal of one or more impurities. Like the '497 patent discussed above, the '885 patent discloses blood levels of drug, such as insulin, following administration, such as via inhalation, and compares these levels with the levels achieved

following subcutaneous injection with the drug. (*see e.g.* col. 10, line 62 until col. 11, line 3, comparing blood levels of insulin following pulmonary administration of insulin in fumaryl diketopiperazine with blood levels of insulin following subcutaneous injection).

However, a discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. (*see e.g.* Patton) The '497 patent does not disclose or suggest administration into a cell, let alone that a complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer. Therefore, claims 1, 4-10, and 13-36, as amended, are not anticipated by the '885 patent.

Rejection Under 35 U.S.C. § 103

Claims 1-36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the '497 patent, in view of the '885 patent. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim

limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The courts have warned that "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

Analysis

The cited references do not recite each and every element of the claims

As discussed above, neither the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, much less how to administer a drug directly to a cell. Therefore, since neither of the references alone discloses at least these elements of the claimed methods, the combination of the '497 patent with the '885 patent does not disclose all of the elements of the claimed methods.

The cited references do not provide one of skill in the art with a reasonable expectation of success

As discussed above, neither the '497 patent nor the '885 patent disclose or suggest delivery of a compound through a cell membrane directly to a cell. The '497 and the '885 patents focus on drug transport through an organ membrane, such as the lung, into the blood stream. The fact that transport of the drug occurred from the lungs into the blood stream does not explicitly or inherently amount to a disclosure of transport into a cell through the cell's membrane. As described in Patton, transport into the blood stream occurs through different paths, including transport between cells. Therefore, one of ordinary skill in the art is not provided with a reasonable expectation of success based on the disclosures in the '497 patent and the '885 patent that a complex of compound and DKP can result in enhanced transport of the compound across a cell membrane and into the cell. Therefore, claims 1 and 3-36, as amended, are not obvious over the '497 and '885 patents.

Additional Amendments to the claims

Claim 1 has been amended to delete "administering with a schedule resulting in substantially no increase in immune response". Claim 2 has been canceled. New claim 38, is a dependent claim, which includes the limitation deleted from claim 1. Support for this amendment can be found in the specification at least in original claim 3. Applicants respectfully point out that previous claim 1 and its dependent claims (as listed in the Amendment filed June 7, 2006) were novel and non-obvious for at least the reasons discussed in the Amendment and Response filed June 7, 2006. However, Applicants amended the claims to advance prosecution of this application. Claim 4 has been amended to depend from new claim 38. Claims 14 and 34 have been amended to more clearly refer to the cell in claim 1 from which they depend.

Allowance of claims 1, 3-36, and 38, as amended, is respectfully solicited.

Respectfully submitted,

/Rivka D. Monheit/
Rivka D. Monheit
Reg. No. 48,731

Date: January 5, 2007

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2152
(404) 879-2160 (Facsimile)